Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

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Guidelines Development Process

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral (ARV) agents in pregnant women for treatment of HIV infection and for prevention of mother-to-child transmission of HIV in the United States.
Panel members	The Panel is composed of approximately 30 voting members who have expertise in management of pregnant HIV-infected women (such as training in either obstetrics/gynecology or women's health) and interventions to prevent mother-to-child transmission (such as specialized training in pediatric HIV infection) as well as community representatives with knowledge of HIV infection in pregnant women and interventions to prevent mother-to-child transmission. The U.S. government representatives, appointed by their agencies, include at least 1 representative from each of the following Department of Health and Human Services (HHS) agencies: the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH). Members who do not represent U.S. government agencies are selected by Panel members after an open announcement to call for nominations. Each member serves on the Panel for a 3-year period, with an option for reappointment. All Panel members are listed on the Panel Roster on Page iv of the guidelines.
Financial disclosures	All members of the Panel submit a written financial disclosure annually reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* Web site (http://aidsinfo.nih.gov).
Users of the guidelines	Providers of care to HIV-infected pregnant women and to HIV-exposed infants
Funding source	Office of AIDS Research (OAR), NIH
Evidence collection	The recommendations in these guidelines are generally based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	See Table 2.
Method of synthesizing data	Each section of the guidelines is assigned to a small group of Panel members with expertise in the area of interest. The members synthesize the available data and propose recommendations to the entire Panel. The Panel discusses and votes on all proposals during monthly teleconferences. Proposals receiving endorsement from a consensus of members are included in the guidelines as official Panel recommendations.
Other guidelines	These guidelines focus on HIV-infected pregnant women and their infants. Other guidelines outline the use of antiretroviral therapy (ART) in nonpregnant HIV-infected adults and adolescents, HIV-infected children, and people who experience occupational or nonoccupational exposure to HIV. The guidelines described are also available on the AIDS*info* Web site (http://www.aidsinfo.nih.gov). Preconception management for nonpregnant women of reproductive age is briefly discussed in this document. However, for more detailed discussion on issues of treatment of nonpregnant adults, the Working Group defers to the designated expertise offered by Panels that have developed those guidelines.
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, new dosing formulations, or changes in dosing frequency), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. In the event of significant new data that may affect patient safety, the Panel may issue a warning announcement and accompanying recommendations on the AIDS*info* Web site until the guidelines can be updated with appropriate changes. Updated guidelines are available at the AIDS*info* Web site (http://www.aidsinfo.nih.gov).
Public comments	A 2-week public comment period follows release of the updated guidelines on the AIDS*info* Web site. The Panel reviews comments received to determine whether additional revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@aidsinfo.nih.gov.

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints **II:** One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes **III:** Expert opinion

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 1 of 6)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
PACTG 076 United States, France[1] Formula feeding	ZDV vs. placebo	Long (from 14 weeks) IV IP	Long (6 weeks), infant only	• MTCT at 18 months was 8.3% in ZDV arm vs. 25.5% in placebo arm (68% efficacy).
CDC short-course ZDV trial Thailand[2] Formula feeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	None	• MTCT at 6 months was 9.4% in ZDV arm vs. 18.9% in placebo arm (50% efficacy).
DITRAME (ANRS 049a) trial Ivory Coast, Burkina Faso[3-4] Breastfeeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	Short (1 week), mother only	• MTCT was 18.0% in ZDV arm vs. 27.5% in placebo arm at 6 months (38% efficacy) and 21.5% vs. 30.6% at 15 months (30% efficacy). • MTCT was 22.5% in ZDV arm vs. 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).
CDC short-course ZDV trial Ivory Coast[4-5] Breastfeeding	ZDV vs. placebo	Short (from 36 weeks) Oral IP	None	• MTCT was 16.5% in ZDV arm vs. 26.1% in placebo arm at 3 months (37% efficacy). • MTCT was 22.5% in ZDV arm vs. 30.2% in placebo arm in pooled analysis at 24 months (26% efficacy).
PETRA trial South Africa, Tanzania, and Uganda[6] Breastfeeding and formula feeding	AP/IP/PP ZDV + 3TC vs. IP/PP ZDV + 3TC vs. IP-only ZDV + 3TC vs. placebo	Short (from 36 weeks) Oral IP	Short (1 week), mother and infant	• MTCT was 5.7% at 6 weeks for AP/IP/PP ZDV + 3TC, 8.9% for IP/PP ZDV + 3TC, 14.2% for IP-only ZDV + 3TC, and 15.3% for placebo (efficacy compared with placebo: 63%, 42%, and 0%, respectively). • MTCT was 14.9% at 18 months for AP/IP/PP ZDV + 3TC, 18.1% for IP/PP ZDV + 3TC, 20.0% for IP-only ZDV + 3TC, and 22.2% for placebo (efficacy compared with placebo: 34%, 18%, and 0%, respectively).
HIVNET 012 trial Uganda[7] Breastfeeding	sdNVP vs. ZDV	No AP ARV Oral IP: sdNVP vs. oral ZDV	sdNVP within 72 hours of birth (infant only) vs. ZDV (1 week), infant only	• MTCT was 11.8% in NVP arm vs. 20.0% in ZDV arm at 6–8 weeks (42% efficacy); 15.7% in NVP arm vs. 25.8% in ZDV arm at 18 months (41% efficacy).

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 2 of 6)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
SAINT trial South Africa[8] Breastfeeding and formula feeding	sdNVP vs. ZDV + 3TC	No AP ARV Oral IP: sdNVP vs. ZDV + 3TC	sdNVP within 48 hours of birth (mother and infant) vs. ZDV + 3TC (1 week), mother and infant	• MTCT was 12.3% in sdNVP arm vs. 9.3% in ZDV + 3TC arm at 8 weeks (difference not statistically significant, P = 0.11).
Perinatal HIV Prevention Trial (PHPT-1) Thailand[9] Formula feeding	Four ZDV regimens with different durations of AP and infant PP administration, no placebo	Long (from 28 weeks), short (from 36 weeks) Oral IP	Long (6 weeks), short (3 days), infant only	• Short-short arm stopped at interim analysis (10.5%). MTCT was 6.5% in long-long arm vs. 4.7% in long-short arm and 8.6% in short-long arm at 6 months (no statistical difference). *In utero* transmission was significantly higher with short vs. long maternal therapy regimens (5.1% vs. 1.6%).
PACTG 316 trial Bahamas, Belgium, Brazil, France, Germany, Italy, Spain, Sweden, Switzerland, United Kingdom, United States[10] Formula feeding	sdNVP vs. placebo among women already receiving ZDV alone (23%) or ZDV + other ARV drugs (77% combination therapy)	Nonstudy ARV regimen Oral IP: placebo vs. sdNVP + IV ZDV	Placebo vs. sdNVP within 72 hours of birth + nonstudy ARV drugs (ZDV), infant only	• 77% of women received dual- or triple-combination ARV regimens during pregnancy. • Trial stopped early due to very low MTCT in both arms: 1.4% in sdNVP arm vs. 1.6% in placebo arm (53% of MTCT was *in utero*).
Perinatal HIV Prevention Trial (PHPT-2) Thailand[11] Formula feeding	ZDV alone vs. ZDV + maternal and infant sdNVP vs. ZDV + maternal sdNVP	ZDV from 28 weeks Oral IP: ZDV alone or ZDV + sdNVP	ZDV for 1 week with or without sdNVP, infant only	• ZDV-alone arm was stopped due to higher MTCT than the NVP-NVP arm (6.3% vs. 1.1%). In arms in which the mother received sdNVP, MTCT rate did not differ significantly between the infant receiving or not receiving sdNVP (2.0% vs. 2.8%).
DITRAME Plus (ANRS 1201.0) trial Ivory Coast[12] Breastfeeding and formula feeding	Open label, ZDV + sdNVP	ZDV from 36 weeks Oral IP: ZDV plus sdNVP	sdNVP + ZDV for 1 week, infant only	• MTCT was 6.5% (95% CI, 3.9%–9.1%) at 6 weeks; MTCT for historical control group receiving short ZDV (98% breastfed) was 12.8%.
DITRAME Plus (ANRS 1201.1) trial Ivory Coast[12] Breastfeeding and formula feeding	Open label, ZDV + 3TC + sdNVP	ZDV + 3TC from 32 weeks (stopped at 3 days PP) Oral IP: ZDV + 3TC + sdNVP	sdNVP + ZDV for 1 week, infant only	• MTCT was 4.7% (95% CI, 2.4%–7.0%) at 6 weeks; MTCT for historical control group receiving short ZDV (98% breastfed) was 12.8%.

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 3 of 6)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
NVAZ trial Malawi[13] Breastfeeding	Neonatal sdNVP vs. sdNVP + ZDV	No AP or IP ARV (latecomers)	sdNVP with or without ZDV for 1 week, infant only	• MTCT was 15.3% in sdNVP + ZDV arm and 20.9% in sdNVP-only arm at 6–8 weeks. MTCT rate at 6–8 weeks among infants who were HIV uninfected at birth was 7.7% and 12.1%, respectively (36% efficacy).
Postnatal NVP + ZDV trial Malawi[14] Breastfeeding	Neonatal sdNVP vs. sdNVP + ZDV	No AP ARV Oral IP: sdNVP	sdNVP with or without ZDV for 1 week, infant only	• MTCT was 16.3% in NVP + ZDV arm and 14.1% in sdNVP-only arm at 6–8 weeks (difference not statistically significant). MTCT rate at 6–8 weeks among infants who were HIV uninfected at birth was 6.5% and 16.9%, respectively.
Post-exposure Infant Prophylaxis South Africa[15] Breastfeeding and formula feeding	Neonatal sdNVP vs. ZDV for 6 weeks	No AP or IP ARV	sdNVP vs. ZDV for 6 weeks	• For formula-fed infants only, MTCT was 14.3% in sdNVP arm vs. 14.1% in ZDV arm at 6 weeks (not significant, $P = 0.30$). For breastfed infants only, MTCT was 12.2% in sdNVP arm and 19.6% in ZDV arm ($P = 0.03$).
Mashi Botswana[16-17] Breastfeeding and formula feeding	**Initial:** short-course ZDV with/without maternal and infant sdNVP and with/without breastfeeding **Revised:** short-course ZDV + infant sdNVP with/without maternal sdNVP and with/without breastfeeding; women with CD4 cell counts <200 cells/mm^3 receive combination therapy	1st randomization ZDV from 34 weeks Oral IP: ZDV + either sdNVP vs. placebo	2nd randomization Breastfeeding + ZDV (infant) 6 months + sdNVP, infant only vs. Formula feeding + ZDV (infant) 4 weeks + sdNVP, infant only	• **Initial design:** In formula-feeding arm, MTCT at 1 month was 2.4% in maternal and infant sdNVP arm and 8.3% in placebo arm (P = 0.05). In breastfeeding + infant ZDV arm, MTCT at 1 month was 8.4% in sdNVP arm and 4.1% in placebo arm (difference not statistically significant). • **Revised design:** MTCT at 1 month was 4.3% in maternal + infant sdNVP arm and 3.7% in maternal placebo + infant sdNVP arm (no significant difference; no interaction with mode of infant feeding). • MTCT at 7 months was 9.1% in breastfeeding + ZDV arm and 5.6% in formula-feeding arm; mortality at 7 months was 4.9% in breastfeeding + ZDV arm vs. 9.3% in formula-feeding arm; HIV-free survival at 18 months was 15.6% breastfeeding + ZDV arm vs. 14.2% formula-feeding arm.

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 4 of 6)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
SWEN Uganda, Ethiopia, India[18] Breastfeeding	sdNVP vs. NVP for 6 weeks	No AP ARV Oral IP: sdNVP	Infant sdNVP vs. NVP for 6 weeks	• Postnatal infection in infants uninfected at birth: - MTCT at 6 weeks was 5.3% in sdNVP arm vs. 2.5% in extended NVP arm (risk ratio 0.54, $P = 0.009$). - MTCT at 6 months was 9.0% in sdNVP arm vs. 6.9% in extended NVP arm (risk ratio 0.80, $P = 0.16$). • HIV-free survival significantly lower in extended NVP arm at both 6 weeks and 6 months of age.
PEPI-Malawi Trial Malawi[19] Breastfeeding	sdNVP + ZDV for 1 week (control) vs. two extended infant regimens (NVP or NVP/ZDV) for 14 weeks	No AP ARV Oral IP: sdNVP (if mother presents in time)	Infant sdNVP + ZDV for 1 week (control) vs. control + NVP for 14 weeks vs. control + NVP/ZDV for 14 weeks	• Postnatal infection in infants uninfected at birth: - MTCT at age 6 weeks was 5.1% in control vs. 1.7% in extended NVP (67% efficacy) and 1.6% in extended NVP/ZDV arms (69% efficacy). - MTCT at age 9 months was 10.6% in control vs. 5.2% in extended NVP (51% efficacy) and 6.4% in extended NVP/ZDV arms (40% efficacy). • No significant difference in MTCT between the extended prophylaxis arms; however, more hematologic toxicity with NVP/ZDV.
MITRA Tanzania[20] Breastfeeding	Infant 3TC for 6 months (observational)	ZDV/3TC from 36 weeks through labor	Maternal ZDV/3TC for 1 week; infant 3TC for 6 months	• MTCT at age 6 months was 4.9% (postnatal MTCT between ages 6 weeks and 6 months was 1.2%).
Kisumu Breastfeeding Study (KiBS) Kenya[21] Breastfeeding	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 cell count >250 cells/mm^3) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 cell count >250 cells/mm^3) for 6 months; infant sdNVP	• MTCT at age 6 months was 5.0% (postnatal MTCT between ages 7 days and 6 months was 2.6%).

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 5 of 6)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
MITRA-PLUS Tanzania[22] Breastfeeding	Maternal triple-drug prophylaxis (observational)	ZDV/3TC/NVP (NFV if CD4 cell count >200 cells/mm^3) from 34 weeks through labor	Maternal ZDV/3TC/NVP (NFV if CD4 cell count >200 cells/mm^3) for 6 months; infant ZDV/3TC for 1 week	• MTCT at age 6 months was 5.0% (postnatal MTCT between ages 6 weeks and 6 months was 0.9%), not significantly different from 6 months infant prophylaxis in MITRA.
Kesho Bora Multi-African[23] Breastfeeding primarily	Antepartum ZDV/sdNVP with no postnatal prophylaxis vs. maternal triple-drug prophylaxis in women with CD4 cell counts of 200–500 cells/mm^3	**Arm 1:** ZDV/3TC/LPV/r **Arm 2:** ZDV + sdNVP From 28 weeks through labor	**Arm 1:** Maternal ZDV/3TC/LPV/r for 6 months; infant sdNVP + ZDV for 1 week **Arm 2:** Maternal ZDV/3TC for 1 week (no further postnatal prophylaxis); infant sdNVP + ZDV for 1 week (no further postnatal prophylaxis)	• MTCT at birth was 1.8% with maternal triple-drug prophylaxis Arm 1 and 2.5% with ZDV/sdNVP Arm 2, not significantly different. In women with CD4 cell counts 350–500 cells/mm^3, MTCT at birth was 1.7% in both arms. • MTCT at age 12 months was 5.4% with maternal triple-drug prophylaxis Arm 1 and 9.5% with ZDV/sdNVP (with no further postnatal prophylaxis after 1 week) Arm 2 (P = 0.029).
Mma Bana Botswana[24] Breastfeeding	Maternal triple-drug prophylaxis (compares 2 regimens) in women with CD4 cell counts >200 cells/mm^3	**Arm 1:** ZDV/3TC/ABC **Arm 2:** ZDV/3TC/LPV/r From 26 weeks through labor	**Arm 1:** Maternal ZDV/3TC/ABC for 6 months; infant sdNVP + ZDV for 4 weeks **Arm 2:** Maternal ZDV/3TC/LPV/r for 6 months; infant sdNVP + ZDV for 4 weeks	• MTCT at age 6 months overall was 1.3%: 2.1% in ZDV/3TC/ABC Arm 1 and 0.4% in ZDV/3TC/LPV/r Arm 2 (P = 0.53).
BAN Malawi[25] Breastfeeding	Postpartum maternal triple-drug prophylaxis vs. infant NVP in women with CD4 cell counts ≥250 cells/mm^3	No AP drugs IP regimens: **Arm 1 (control):** ZDV/3TC + sdNVP **Arm 2:** ZDV/3TC + sdNVP **Arm 3:** ZDV/3TC + sdNVP	**Arm 1 (control):** Maternal ZDV/3TC for 1 week; infant sdNVP + ZDV/3TC for 1 week **Arm 2:** Control as above, then maternal ZDV/3TC/LPV/r for 6 months **Arm 3:** Control as above, then infant NVP for 6 months	• Postnatal infection in infants uninfected at age 2 weeks: - MTCT at age 28 weeks was 5.7% in control Arm 1; 2.9% in maternal triple-drug prophylaxis Arm 2 (P = 0.009 vs. control); 1.7% in infant NVP Arm 3 (P <0.001 vs. control). • No significant difference between maternal triple-drug prophylaxis Arm 2 and infant NVP Arm 3 (P = 0.12).

Table 3. Results of Major Studies on Antiretroviral Prophylaxis to Prevent Mother-to-Child Transmission of HIV (page 6 of 6)

Study Location(s) Mode of Infant Feeding	Antiretroviral (ARV) Drugs	Antepartum and Intrapartum	Postpartum	Mother-to-Child Transmission (MTCT) Rate and Efficacy
HPTN 046[26] South Africa, Tanzania, Uganda, Zimbabwe Breastfeeding	Postpartum prophylaxis of breast milk transmission of HIV with 6 weeks vs. 6 months of infant NVP	AP drugs allowed if required for maternal health	All infants received daily NVP from birth through age 6 weeks. **Arm 1:** Daily infant NVP from 6 weeks through 6 months of age **Arm 2:** Daily infant placebo from 6 weeks through age 6 months of age	• In infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 1.1% (0.3–1.8%) in the extended NVP Arm 1 and 2.4% (1.3–3.6%) in the placebo Arm 2 (P = 0.048). • At infant randomization at age 6 weeks, 29% of mothers in each arm were receiving a triple-ARV regimen for treatment of HIV. • For mothers receiving triple-ARV drugs at the time of randomization, in infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 0.2% and not statistically different between extended NVP Arm 1 (0.5%) and placebo Arm 2 (0%). • For mothers with CD4 cell counts >350 cells/mm^3 who were not receiving triple ARV drugs, in infants uninfected at age 6 weeks, the 6-month infant HIV infection rate was 0.7% (0–1.5%) in the extended NVP Arm 1 and 2.8% (1.3 – 4.4%) in the placebo Arm 2 (*P* = 0.014).
NICHD-HPTN 040/PACTG 1043 Argentina, Brazil, South Africa, U.S.[27] Formula feeding	Infant prophylaxis with 6 weeks ZDV vs. 6 weeks infant ZDV plus three doses of NVP in first week of life vs. 6 weeks infant ZDV plus 2 weeks of 3TC/NFV	No AP drugs If mother presented early enough, IV ZDV during labor through delivery	**Arm 1 (control):** Infant ZDV for 6 weeks **Arm 2:** Control as above plus NVP with first dose within 48 hours of birth, second dose 48 hours later, and third dose 96 hours after the second dose **Arm 3:** Control as above, plus 3TC and NFV from birth through 2 weeks of age	• Intrapartum HIV transmission among infants with negative HIV test at birth: 4.8% (3.2–7.1%) ZDV (Arm 1) vs. 2.2% (1.2–3.9%) in ZDV plus NVP (Arm 2) (*P* = 0.046 compared with Arm 1) vs. 2.4% (1.4–4.3%) in ZDV plus 3TC/NFV (Arm 3) (*P* = 0.046 compared with Arm 1). • Overall HIV transmission rates, including in utero infection: 11.0% (8.7–14.0%) ZDV (Arm 1) vs. 7.1% (5.2–9.6%) in ZDV plus NVP (Arm 2) (*P* = 0.035 compared with Arm 1) vs. 7.4% (5.4–9.9%) in ZDV plus 3TC/NFV (Arm 3) (*P* = 0.035 compared with Arm 1). • Grade 3 or 4 neutropenia more frequent in ZDV/3TC/NFV Arm 3, 70 infants, compared with ZDV alone Arm 1, 33 infants, or ZDV/NVP Arm 2, 32 infants (*P* <0.001).

Key to Abbreviations: 3TC = lamivudine; ABC = abacavir; AP = antepartum; ARV = antiretroviral; CDC = Centers for Disease Control and Prevention; CI = confidence interval; IP = intrapartum; IV = intravenous; LPV/r = lopinavir/ritonavir; MTCT = mother-to-child transmission; NFV = nelfinavir; NVP = nevirapine; PP = postpartum; sd = single-dose; ZDV = zidovudine

Table 4: Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (Page 1 of 2)

Antiretroviral (ARV) Drug	Effect on Drug Levels	Dosing Recommendation/ Clinical Comment
Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)		
Efavirenz (EFV)	Oral ethinyl estradiol/norgestimate: No effect on ethinyl estradiol concentrations;↓ active metabolites of norgestimate (levonorgestrel AUC ↓83%; norelgestromin AUC ↓64%)	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. EFV had no effect on ethinyl estradiol concentrations, but progestin levels (norelgestromin and levonorgestrel) were markedly decreased. No effect of ethinyl estradiol/norgestimate on EFV plasma concentrations was observed.
	Implant: ↓ etonogestrel	A reliable method of barrier contraception must be used in addition to hormonal contraceptives. The interaction between etonogestrel and EFV has not been studied. Decreased exposure of etonogestrel may be expected. There have been postmarketing reports of contraceptive failure with etonogestrel in EFV-exposed patients.
	Levonorgestrel AUC ↓58%	Effectiveness of emergency postcoital contraception may be diminished.
Etravirine (ETR)	Ethinyl estradiol AUC ↑22% Norethindrone: no significant effect	No dosage adjustment necessary.
Nevirapine (NVP)	Ethinyl estradiol AUC ↓20% Norethindrone AUC ↓19% DMPA: no significant change	Use alternative or additional methods. No dosage adjustment needed.
Ritonavir (RTV)-boosted Protease Inhibitor (PI)		
Atazanavir/ritonavir (ATV/r)	↓ Ethinyl estradiol ↑ Norgestimate	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
Darunavir/ritonavir (DRV/r)	Ethinyl estradiol AUC ↓44% Norethindrone AUC ↓14%	Use alternative or additional method.
Fosamprenavir/ritonavir (FPV/r)	Ethinyl estradiol AUC ↓37% Norethindrone AUC ↓34%	Use alternative or additional method.
Lopinavir/ritonavir (LPV/r)	Ethinyl estradiol AUC ↓42% Norethindrone AUC ↓17%	Use alternative or additional method.
Saquinavir/ritonavir (SQV/r)	↓Ethinyl estradiol	Use alternative or additional method.
Tipranavir/ritonavir (TPV/r)	Ethinyl estradiol AUC ↓48% Norethindrone: no significant change	Use alternative or additional method.

Table 4: Drug Interactions Between Antiretroviral Agents and Hormonal Contraceptives (Page 2 of 2)

Antiretroviral (ARV) Drug	Effect on Drug Levels	Dosing Recommendation/ Clinical Comment
PI without RTV		
Atazanavir (ATV)	Ethinyl estradiol AUC↑48% Norethindrone AUC ↑110%	Oral contraceptive should contain no more than 30 mcg of ethinyl estradiol or use alternative method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
Fosamprenavir (FPV)	With APV: ↑ Ethinyl estradiol and ↑ norethindrone; ↓APV 20%	Use alternative method.
Indinavir (IDV)	Ethinyl estradiol AUC ↑25% Norethindrone AUC ↑26%	No dose adjustment.
Nelfinavir (NFV)	Ethinyl estradiol AUC ↓47% Norethindrone AUC ↓18%	Use alternative or additional method.
CCR5 Antagonist		
Maraviroc (MVC)	No significant effect on ethinyl estradiol or levonorgestrel	Safe to use in combination.

Key to Abbreviations: AUC = area under the curve; DMPA = depot medroxyprogesterone acetate

Derived from: Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services. January 10, 2011; pp. 1–166; Tables 15a, 15b, and 15d. Accessed August 31, 2011. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Updated September 14, 2011; Erratum issued December 1, 2011. Page 1 of 11.)

(See also Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy supplement for additional toxicity data and Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents for detailed guidelines regarding treatment options.)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
NRTIs			NRTIs are recommended for use as part of combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection.		See text for discussion of potential maternal and infant mitochondrial toxicity.
Preferred Agents					
Lamivudine (3TC) Epivir	**Epivir** 150-, 300-mg tablets or 10-mg/mL oral solution **Combivir** 3TC 150 mg + ZDV 300 mg **Epzicom** 3TC 300 mg + ABC 600 mg **Trizivir**‡ 3TC 150 mg + ZDV 300 mg + ABC 300 mg	**Epivir** 150 mg BID or 300 mg once daily Take without regard to meals. **Combivir** 1 tablet BID **Epzicom** 1 tablet once daily **Trizivir** 1 tablet BID	Because of extensive experience with 3TC in pregnancy in combination with ZDV, 3TC plus ZDV is the recommended dual-NRTI backbone for pregnant women.	PK not significantly altered in pregnancy; no change in dose indicated[3]. High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects)[4]. Well-tolerated, short-term safety demonstrated for mothers and infants. If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum, see Special Considerations: Hepatitis B Virus Coinfection.
Zidovudine (AZT, ZDV) Retrovir	**Retrovir** 100-mg capsules, 300-mg tablets, 10-mg/mL IV solution, 10-mg/mL oral solution **Combivir** ZDV 300 mg + 3TC 150 mg **Trizivir**‡ ZDV 300 mg + 3TC 150 mg + ABC 300 mg	**Retrovir** 300 mg BID or 200 mg TID Take without regard to meals. **Combivir** 1 tablet BID **Trizivir** 1 tablet BID	Preferred NRTI for use in combination ARV regimens in pregnancy based on efficacy studies and extensive experience; should be included in the antenatal ARV regimen unless there is severe toxicity, d4T use, documented resistance, or the woman is already on a fully suppressive regimen.	PK not significantly altered in pregnancy; no change in dose indicated[5]. High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 1.5-fold increase in overall birth defects)[4]. Well-tolerated, short-term safety demonstrated for mothers and infants.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 2 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Alternative Agents					
Abacavir (ABC) Ziagen	**Ziagen** 300-mg tablets or 20-mg/mL oral solution **Epzicom** ABC 600 mg + 3TC 300 mg **Trizivir**‡ ABC 300 mg + ZDV 300 mg + 3TC 150 mg	**Ziagen** 300 mg BID or 600 mg once daily Take without regard to meals. **Epzicom** 1 tablet once daily **Trizivir** 1 tablet BID	Alternative NRTI for dual-NRTI backbone of combination regimens. See footnote regarding use in triple-NRTI regimen.‡	PKs not significantly altered in pregnancy; no change in dose indicated[6]. High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. Hypersensitivity reactions occur in ~5%–8% of nonpregnant persons; a much smaller percentage are fatal and are usually associated with rechallenge. Rate in pregnancy unknown. Testing for HLA-B*5701 identifies patients at risk of reactions[7-8] and should be done and documented as negative before starting ABC. Patients should be educated regarding symptoms of hypersensitivity reaction.
Didanosine (ddI) Videx EC, generic didanosine enteric coated (EC) (dose same as Videx EC)	**Videx EC** 125-, 200-, 250-, 400-mg capsules Buffered tablets (non-EC) no longer available **Videx** 10-mg/mL oral solution	**Body weight ≥60kg:** 400 mg once daily; with TDF, 250 mg once daily **Body weight <60kg**: 250 mg once daily; with TDF, 200 mg once daily Take 1/2 hour before or 2 hours after a meal Preferred dosing with oral solution is BID (total daily dose divided into 2 doses)	Alternative NRTI for dual-NRTI backbone of combination regimens. ddI should not be used with d4T.	PKs not significantly altered in pregnancy; no change in dose indicated[9]. Moderate placental transfer to fetus.	Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together[10-11].

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 3 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Emtricitabine (FTC) Emtriva	**Emtriva** 200-mg hard gelatin capsule or 10-mg/mL oral solution **Truvada** FTC 200 mg + TDF 300 mg **Atripla** FTC 200 mg + EFV§ 600 mg + TDF 300 mg	**Emtriva** 200-mg capsule once daily or 240 mg (24 mL) oral solution once daily Take without regard to meals. **Truvada** 1 tablet once daily **Atripla** 1 tablet at or before bedtime. Take on an empty stomach to reduce side effects.	Alternative NRTI for dual-NRTI backbone of combination regimens.	PK study shows slightly lower levels in third trimester, compared with postpartum[12]. No clear need to increase dose. High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum, see Special Considerations: Hepatitis B Coinfection.
Stavudine (d4T) Zerit	**Zerit** 15-, 20-, 30-, 40-mg capsules or 1-mg/mL oral solution	**Body weight ≥60 kg:** 40 mg BID **Body weight <60 kg:** 30 mg BID Take without regard to meals. WHO recommends 30-mg BID dosing regardless of body weight.	Alternate NRTI for dual-NRTI backbone of combination regimens. d4T should not be used with ddI or ZDV.	PKs not significantly altered in pregnancy; no change in dose indicated[13]. High placental transfer.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. Lactic acidosis, sometimes fatal, has been reported in pregnant women receiving ddI and d4T together[10-11].

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 4 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Tenofovir Disoproxil Fumarate (TDF) Viread	**Viread** 300-mg tablet **Truvada** TDF 300 mg + FTC 200 mg **Atripla** TDF 300 mg + EFV§ 600 mg + + FTC 200 mg	**Viread** 1 tablet once daily Take without regard to meals. **Truvada** 1 tablet once daily **Atripla** 1 tablet at or before bedtime Take on an empty stomach to reduce side effects.	Alternative NRTI for dual-NRTI backbone of combination regimens. TDF would be a preferred NRTI in combination with 3TC or FTC in women with chronic HBV infection. Because of potential for renal toxicity, renal function should be monitored.	AUC lower in third trimester than postpartum but trough levels adequate[14]. High placental transfer.[15-18].	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. Studies in monkeys at doses approximately 2-fold higher than that for human therapeutic use show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy[19]. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown[20-21]. Significant placental passage in humans (cord:maternal blood ratio 0.6–0.99). If hepatitis B coinfected, possible hepatitis B flare if drug stopped postpartum, see Special Considerations: Hepatitis B Virus Coinfection.
NNRTIs			NNRTIs are recommended for use in combination regimens with 2 NRTI drugs.		Hypersensitivity reactions, including hepatic toxicity, and rash more common in women; unclear if increased in pregnancy.
Preferred Agents					
Nevirapine (NVP) Viramune	200-mg tablets or 50-mg/5-mL oral suspension	200 mg once daily for 14 days (lead-in period); thereafter, 200 mg BID Take without regard to meals. Repeat lead-in period if therapy is discontinued for >7 days. In patients who develop mild-to-moderate rash without constitutional symptoms during lead-in, continue lead-in dosing until rash resolves, but not >28 days total.	NVP should be initiated in pregnant women with CD4 counts >250 cells/mm^3 only if benefit clearly outweighs risk because of the increased risk of potentially life-threatening hepatotoxicity in women with high CD4 cell counts. Women who enter pregnancy on NVP regimens and are tolerating them well may continue therapy, regardless of CD4 count.	PK not significantly altered in pregnancy; no change in dose indicated [22-24]. High placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 cell counts >250/mm^3 when first initiating therapy[25-26]; unclear if pregnancy increases risk.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 5 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Use in Special Circumstances					
Efavirenz§ (EFV) Sustiva	50-, 200-mg capsules or 600- mg tablets **Atripla** EFV§ 600 mg + FTC 200 mg + TDF 300 mg	600 mg once daily at or before bedtime Take on an empty stomach to reduce side effects. **Atripla** 1 tablet once daily at or before bedtime	Use of EFV should be avoided in the first trimester. Use after the first trimester can be considered if, after consideration of other alternatives, this is the best choice for a specific woman. If EFV is to be continued postpartum, adequate contraception must be assured. Women of childbearing age must be counseled regarding the teratogenic potential of EFV and avoidance of pregnancy while on the drug. Because of the known failure rates of contraceptive methods, alternative ARV regimens should be strongly considered in women of childbearing potential.	AUC decreased during third trimester, compared with postpartum, but nearly all third-trimester subjects exceeded target exposure and no change in dose is indicated[27]. Moderate placental transfer to fetus.	FDA Pregnancy Class D; significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 of 20 infants (15%) born to cynomolgus monkeys receiving EFV during the first trimester at a dose resulting in plasma levels comparable to systemic human therapeutic exposure. There are 6 retrospective case reports and 1 prospective case report of neural tube defects in humans with first-trimester exposure and 1 prospective case of anophthalmia with facial clefts[28-30]; relative risk unclear.
Insufficient Data to Recommend Use					
Etravirine (ETR) Intelence	100-, 200-mg tablets	200 mg BID Take following a meal.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy.	No PK studies in human pregnancy, placental transfer rate unknown.	No experience in human pregnancy.
Rilpivirine (RPV) Endurant	25-mg tablets **Complera** RPV 25 mg + TDF 300 mg + FTC 200 mg	25 mg once daily with a meal. **Complera** 1 tablet once daily	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy.	No PK studies in human pregnancy, placental transfer rate unknown.	No experience in human pregnancy.
PIs			PIs are recommended for use in combination regimens with 2 NRTI drugs.		Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs (see Protease Inhibitor Therapy and Hyperglycemia).

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 6 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Preferred Agents					
Lopinavir + Ritonavir (LPV/r) Kaletra	**Tablets:** (LPV 200 mg + RTV 50 mg) or (LPV 100 mg + RTV 25 mg) **Oral solution:** Each 5 mL contains (LPV 400 mg + RTV 100 mg) Oral solution contains 42% alcohol	LPV/r 400 mg/100 mg BID **Second/Third trimester:** Some experts recommend increased dose LPV/r 600 mg/150 mg BID in the second and third trimester[1] **With EFV or NVP (PI-naive or PI-experienced patients):** LPV/r 500 mg/125 mg tablets BID (use a combination of two LPV/r 200 mg/50 mg tablets + one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125 mg.) or LPV/r 533 mg/133 mg oral solution (6.5 mL) BID **Tablets:** Take without regard to meals. **Oral solution:** Take with food. **Not used in pregnancy:** Adult dosage of LPV/r 800 mg/200 mg once daily is not recommended for use in pregnancy.	PK studies suggest dose should be increased to 600 mg/150 mg BID in second and third trimester, especially in PI-experienced patients. If standard dosing is used, monitor virologic response and LPV drug levels, if available. Once-daily LPV/r dosing is not recommended during pregnancy because there are no data to address whether drug levels are adequate with such administration.	AUC decreased in second and third trimester with standard dosing[31-33]. AUC with dose of LPV/r 600 mg/150 mg twice daily in third trimester in women in the United States resulted in AUC similar to that in nonpregnant adults taking LPV/r 400 mg/100 mg dose twice daily[12]. Low placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. Well-tolerated, short-term safety demonstrated in Phase I/II studies.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 7 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Alternative Agents					
Atazanavir (ATV) Reyataz (combined with low-dose RTV boosting)	100-, 150-, 200-, 300-mg capsules	ATV 300 mg + RTV 100 mg once daily Some experts recommend increased dose (ATV 400 mg + RTV 100 mg once daily) in all pregnant women in the second and third trimesters ATV package insert recommends increased dose (ATV 400 mg + RTV 100 mg once daily) in the following situations: - With TDF or H2-receptor antagonist (not both; use of both with ATV not recommended) in ARV-experienced pregnant patients - With EFV in ARV-naive patients (Concurrent use of ATV with EFV in ARV-experienced patients not recommended due to decreased ATV levels) Take with food.[1]	Alternative PI for use in combination regimens in pregnancy. Should give as low-dose RTV-boosted regimen, may use once daily dosing. A study of 41 pregnant women described in the package insert for Reyataz concluded that no dose adjustment of ATV was needed for the majority of pregnant women infected with strains of HIV susceptible to ATV. The exception was in ART-experienced pregnant women on either tenofovir or H2-receptor blocker (not both) who should receive increase in ATV dose to 400 mg (with ritonavir 100 mg).	Two of three intensive PK studies of ATV with RTV boosting during pregnancy and the PK study described in the recently approved product label suggest that standard dosing results in decreased plasma concentrations, compared with nonpregnant adults[15, 34-36]. However, for most pregnant women (not on interacting concomitant medications), no dose adjustment was needed. ATV concentrations further reduced ~25% with concomitant TDF use[15, 36]. Low placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4]. Transplacental passage is low, with cord blood concentration averaging 10%–19% of the maternal delivery ATV concentration[15, 34, 36]. Theoretical concern regarding increased indirect bilirubin levels causing significant exacerbation in physiologic hyperbilirubinemia in neonates has not been observed in clinical trials to date[15, 34-37].
Ritonavir (RTV) Norvir	100-mg capsules 100-mg tablets 80-mg/mL oral solution Oral solution contains 43% alcohol	**As PK booster for other PIs:** 100–400 mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations) **Tablets:** Take with food. **Capsule and oral solution:** Take with food if possible, which may improve tolerability.	Given low levels in pregnant women when used alone, should only be used in combination with second PI as low-dose RTV "boost" to increase levels of second PI.	Phase I/II study in pregnancy showed lower levels during pregnancy compared with postpartum[38]. Minimal placental transfer to fetus.	Limited experience at full dose in human pregnancy; has been used as low-dose RTV boosting with other PIs. No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[4].

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 8 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Saquinavir (SQV) Invirase (Available as hard gelatin capsules and tablets. SQV must be combined with low-dose RTV boosting.)	500-mg tablets or 200-mg hard gelatin capsules	(SQV 1,000 mg + RTV 100 mg) BID Unboosted SQV is **not** recommended. Take with meals or within 2 hours after a meal.	PK data on SQV hard gelatin capsules and the new tablet formulation in pregnancy are limited. RTV-boosted SQV hard gelatin capsules or SQV tablets are alternative PIs for combination regimens in pregnancy and are alternative initial ARV recommendations for nonpregnant adults. Must give as low-dose RTV-boosted regimen.	Limited PK data on SQV hard gelatin capsules and the new 500-mg tablet formulation suggest that 1,000 mg SQV hard gelatin capsules/100 mg RTV given twice daily achieves adequate SQV drug levels in pregnant women[39]. Minimal placental transfer to fetus.	Well-tolerated, short-term safety demonstrated for mothers and infants for SQV in combination with low-dose RTV. Baseline EKG recommended before starting because PR and/or QT interval prolongations have been observed.
Use in Special Circumstances					
Indinavir (IDV) Crixivan (combined with low-dose RTV boosting)	100-, 200-, 400- mg capsules	**With RTV:** (IDV 800 mg + RTV 100– 200 mg) BID Take without regard to meals. **Not used in pregnancy:** Adult dosage of IDV (without RTV) 800 mg every 8 hours is not recommended for use in pregnancy.	Because of twice-daily dosing, pill burden, and potential for renal stones, IDV should only be used when preferred and alternative agents cannot be used. Must give as low-dose RTV-boosted regimen.	Two studies including 18 women receiving IDV 800 mg three times daily showed markedly lower levels during pregnancy compared with postpartum, although suppression of HIV RNA levels was seen[40-41]. In a study of RTV-boosted IDV (400 mg IDV/100 mg RTV twice daily), 82% of women met the target trough level[42]. Minimal placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[28]. Theoretical concern regarding increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in neonates, but minimal placental passage. Use of unboosted IDV during pregnancy is not recommended.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 9 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Nelfinavir (NFV) Viracept	250-, 625-mg tablets 50-mg/g oral powder	1,250 mg BID Take with food. **Not used in pregnancy:** Adult dosage of NFV 750 mg TID is not recommended for use in pregnancy.	Given PK data and extensive experience with use in pregnancy, NFV might be considered in special circumstances for prophylaxis of transmission in women in whom therapy would not otherwise be indicated when alternative agents are not tolerated. In clinical trials of initial therapy in nonpregnant adults, NFV-based regimens had a lower rate of viral response compared with LPV/r or EFV-based regimens, but similar viral response to ATVor NVP-based regimens.	Adequate drug levels are achieved in pregnant wome with NFV 1,250 mg given twice daily, although levels are variable in late pregnancy[23, 43-44]. In a study of pregnant women in their second and third trimester dosed at 1,250 mg given twice daily, women in the third trimester had lower concentration of NFV than women in the second trimester[44]. In a study of the new 625-mg tablet formulation dosed at 1,250 mg twice daily, lower AUC and peak levels were observed during the third trimester of pregnancy than postpartum[45]. Minimal to low placental transfer to fetus.	No evidence of human teratogenicity (can rule out 2-fold increase in overall birth defects)[28]. Well-tolerated, short-term safety demonstrated for mothers and infants.
Insufficient Data to Recommend Use					
Darunavir (DRV) Prezista (must be combined with low-dose RTV boosting)	75-, 150-, 400-, 600-mg tablets	**ARV-naive patients:** (DRV 800 mg + RTV 100 mg) once daily **ARV-experienced patients:** (DRV 800 mg + RTV 100 mg) once daily if no DRV resistance mutations (DRV 600 mg + RTV 100 mg) BID if any DRV resistance mutations Unboosted DRV is **not** recommended. Take with food.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy in ARV-naive patients. Must give as low-dose RTV-boosted regimen.	No PK studies in human pregnancy. Minimal to low placental transfer to fetus[46].	No experience in human pregnancy.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 10 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Fosamprenavir (FPV) Lexiva (a prodrug of amprenavir) (recommended to be combined with low-dose RTV boosting)	700-mg tablet or 50-mg/mL oral suspension	**ARV-naive patients:** • FPV 1,400 mg BID or • (FPV 1,400 mg + RTV 100–200 mg) once daily or • (FPV 700 mg + RTV 100 mg) BID **PI-experienced patients (once-daily dosing not recommended):** • (FPV 700 mg + RTV 100 mg) BID **With EFV:** • (FPV 700 mg + RTV 100 mg) BID or • (FPV 1,400 mg + RTV 300 mg) once daily **Tablet:** Take without regard to meals (if not boosted with RTV tablet). **Suspension:** Take without food. **FPV with RTV tablet:** Take with meals.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy in ARV-naive patients. Recommended to be given as low-dose RTV-boosted regimen.	With RTV boosting, AUC is reduced during the third trimester. However, exposure is greater during the third trimester with boosting than in nonpregnant adults without boosting and trough concentrations achieved during the third trimester were adequate for patients without PI resistance mutations[47]. Low placental transfer to fetus.	Limited experience in human pregnancy.
Tipranavir (TPV) Aptivus (must be combined with low-dose RTV boosting)	250-mg capsules or 100-mg/mL oral solution	(TPV 500 mg + RTV 200 mg) BID Unboosted TPV is **not** recommended. **TPV taken with RTV tablets:** Take with meals. **TPV taken with RTV capsules or solution:** Take without regard to meals.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy in ARV-naive patients. Must give as low-dose RTV-boosted regimen.	No PK studies in human pregnancy. Unknown rate of placental transfer to fetus.	No experience in human pregnancy.

Table 5. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy (Page 11 of 11)

ARV Drug Generic Name (Abbreviation) Trade Name	Formulation	Dosing Recommendations*	Recommendations for Use in Pregnancy	PKs in Pregnancy†	Concerns in Pregnancy
Entry Inhibitors					
Insufficient Data to Recommend Use					
Enfuvirtide (T20) Fuzeon	• Injectable— supplied as lyophilized powder • Each vial contains 108 mg of T20; reconstitute with 1.1 mL of sterile water for injection for delivery of approximately 90 mg/1 mL	90 mg (1mL) SQ BID	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy in ARV-naive patients.	No PK studies in human pregnancy. No placental transfer to fetus, based on very limited data.	Minimal data in human pregnancy[48].
Maraviroc (MVC) Selzentry	150-, 300-mg tablets	• 150 mg BID when given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r) • 300 mg BID when given with NRTIs, T-20, TPV/r, NVP, and other drugs that are not strong CYP3A inhibitors or inducers • 600 mg BID when given with CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) Take without regard to meals.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy in ARV-naive patients.	No PK studies in human pregnancy. Unknown placental transfer rate to fetus.	No experience in human pregnancy
Integrase Inhibitors					
Insufficient Data to Recommend Use					
Raltegravir (RAL) Isentress	400-mg tablets	400 mg BID With rifampin: 800 mg BID Take without regard to meals.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy.	During third trimester, RAL PK show extensive variability but RAL exposure was not consistently altered, compared with postpartum and historical data. The standard dose appears appropriate during pregnancy[49]. Variable but high placental transfer to fetus.	No experience in human pregnancy.

Key to Abbreviations: ARV = antiretroviral; AUC = area under the curve; BID = twice daily; CYP = cytochrome P; EKG = electrocardiogram; FDA = Food and Drug Administration; IV = intravenous; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; PPI = proton pump inhibitor; SQ = subcutaneous injection; TID = three times daily; WHO = World Health Organization

* Dosage should be adjusted in renal or hepatic insufficiency (see Adult Guidelines, Appendix B, Table 7).

[1] Erratum issued December 1, 2011

‡ Triple-NRTI regimens including abacavir have been less potent virologically compared with PI-based combination ARV drug regimens. Triple-NRTI regimens should be used only when an NNRTI- or PI-based combination regimen cannot be used, such as because of significant drug interactions.

§ See section on Teratogenicity for discussion of efavirenz and risks in pregnancy.

† Placental transfer categories—Mean or median cord blood/maternal delivery plasma drug ratio:
High: >0.6
Moderate: 0.3–0.6
Low: 0.1–0.3
Minimal: <0.1

Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States (Page 1 of 4)

Clinical Scenario	Recommendations
Nonpregnant HIV-infected women of childbearing potential who have indications for initiating antiretroviral therapy (ART)	Initiate combination antiretroviral (ARV) drug therapy as per adult treatment guidelines. When feasible, include one or more nucleoside reverse transcriptase inhibitors (NRTIs) with good placental passage as a component of the ARV regimen. • Avoid drugs with teratogenic potential (e.g., efavirenz) in women who are trying to conceive or are not using adequate contraception. Exclude pregnancy and ensure access to effective contraception before starting treatment with efavirenz.
HIV-infected women on combination ARV drug therapy who become pregnant	**Women:** • In general, in women who require treatment, ARV drugs should not be stopped during the first trimester or during pregnancy. • Continue current combination ART, if successfully suppressing viremia; however, avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (e.g., combination stavudine/didanosine) throughout the pregnancy. • Perform HIV ARV drug-resistance testing in women on therapy who have detectable viremia. • Continue combination ART regimen during the intrapartum period (zidovudine given as continuous infusion[a] during labor while other ARV agents are continued orally) and postpartum. • Schedule cesarean delivery at 38 weeks of gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery. **Infants:** • Start zidovudine as soon as possible after birth and administer for 6 weeks.[b]

HIV-infected pregnant women who are ARV naive *and* have indications for ART	**Women:**
	• Perform HIV ARV drug-resistance testing prior to initiating combination ARV drug therapy and repeat after initiating therapy if viral suppression is suboptimal.
	• Initiate combination ARV regimen.
	  • Avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (e.g., combination stavudine/didanosine) throughout the pregnancy.
	  • When feasible, include one or more NRTIs with good placental passage in the ARV regimen.
	  • Use nevirapine as a component of the ARV regimen only in women who have CD4 counts ≤250 cells/mm^3. Because of the increased risk of severe hepatic toxicity, use nevirapine in women with CD4 counts >250 cells/mm^3 only if the benefit clearly outweighs the risk.
	• In women who require initiation of therapy for their own health, initiate treatment as soon as possible, including in the first trimester.
	• Continue the combination regimen during the intrapartum period (zidovudine given as continuous infusion[a] during labor while other ARV agents are continued orally) and postpartum.
	• Schedule cesarean delivery at 38 weeks of gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery.
	Infants:
	• Start zidovudine as soon as possible after birth and administer for 6 weeks.[b]

Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States (Page 2 of 4)

Clinical Scenario	Recommendations

HIV-infected pregnant women who are ARV naive and do *not* require treatment for their own health	**Women:**
	• Perform HIV ARV drug-resistance testing prior to initiating combination ARV drug therapy and repeat after initiation of therapy if viral suppression is suboptimal.
	• Prescribe combination ARV drug prophylaxis (i.e., at least 3 drugs) to prevent perinatal transmission.
	  • Delayed initiation of prophylaxis until after the first trimester of pregnancy can be considered in women who are receiving ARV drugs solely for prevention of perinatal transmission, but earlier initiation of prophylaxis may be more effective in reducing perinatal transmission of HIV.
	  • Avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for mother (e.g., combination stavudine/didanosine) throughout the pregnancy.
	  • When feasible, use one or more NRTIs with good transplacental passage as a component of the ARV regimen.
	  • Use nevirapine as a component of therapy in women who have CD4 counts >250 cells/mm^3 only if the benefit clearly outweighs the risk because of the drug's association with an increased risk of severe hepatic toxicity.
	• Continue ARV prophylaxis regimen during the intrapartum period (zidovudine given as continuous infusion[a] during labor while other ARV agents are continued orally).
	• Evaluate need for continuing the combination regimen postpartum. Following delivery, considerations for continuation of the mother's ARV regimen are the same as for other nonpregnant individuals (see General Principles Regarding Use of Antiretroviral Drugs in Pregnancy). If treatment is to be stopped and the regimen includes a drug with a long half-life, such as a non-nucleoside reverse transcriptase inhibitor (NNRTI), consider stopping NRTIs at least 7 days after stopping NNRTI. (See Stopping Antiretroviral Therapy Drugs During Pregnancy and Prevention of Antiretroviral Drug Resistance.)
	• Schedule cesarean delivery at 38 weeks of gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery.
	Infants:
	• Start zidovudine as soon as possible after birth and administer for 6 weeks.[b]

Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States (Page 3 of 4)

Clinical Scenario	Recommendations

HIV-infected pregnant women who are ARV experienced but not currently receiving ARV drugs	**Women:**
	• Obtain full ARV drug history, including prior resistance testing, and evaluate need for ART for maternal health.
	• Test for HIV ARV drug resistance before re-initiating ARV prophylaxis or therapy and retest after initiating combination ARV regimen if viral suppression is suboptimal.
	• Initiate a combination ARV regimen (e.g., at least 3 drugs), with regimen chosen based on results of resistance testing and history of prior therapy.
	  • In women who require initiation of therapy for their own health, initiate treatment as soon as possible, including in the first trimester.
	  • Delayed initiation of prophylaxis until after the first trimester of pregnancy can be considered in women who are receiving ARV drugs solely for prevention of perinatal transmission, but earlier initiation of prophylaxis may be more effective in reducing perinatal transmission of HIV.
	  • Avoid use of efavirenz or other potentially teratogenic drugs in the first trimester and drugs with known adverse potential for the mother (e.g., combination stavudine/didanosine) throughout the pregnancy.
	  • When feasible, include one or more NRTIs with good transplacental passage as a component of the ARV regimen.
	  • Use nevirapine as a component of therapy in women who have CD4 counts >250 cells/mm^3 only if the benefit clearly outweighs the risk because of the drug's association with an increased risk of severe hepatic toxicity.
	• Continue the combination regimen during intrapartum period (zidovudine given as continuous infusion[a] during labor while other ARV agents are continued orally).
	• Evaluate need for continuing the combination regimen postpartum. Following delivery, considerations for continuation of the mother's ARV regimen are the same as for other nonpregnant adults (see General Principles Regarding Use of Antiretroviral Drugs in Pregnancy). If treatment is to be stopped and the regimen includes a drug with a long half-life, such as NNRTIs, consider stopping NRTIs at least 7 days after stopping NNRTIs. (See Stopping Antiretroviral Therapy and Prevention of Antiretroviral Drug Resistance.)
	• Schedule cesarean delivery at 38 weeks of gestation if plasma HIV RNA remains >1,000 copies/mL near the time of delivery.
	Infants:
	• Start zidovudine as soon as possible after birth and administer for 6 weeks.[b]

HIV-infected women who have received no ART before labor	**Women:** Give zidovudine as continuous infusion[1] during labor. **Infants:** Infants born to HIV-infected women who have not received antepartum ARV drugs should receive prophylaxis with a combination ARV drug regimen started as close to the time of birth as possible. Zidovudine[b] given for 6 weeks combined with 3 doses of nevirapine in the first week of life (at birth, 48 hours later, and 96 hours after the second dose) has been shown to be effective in a randomized controlled trial and less toxic than a 3-drug regimen with nelfinavir and lamivudine for 2 weeks and 6 weeks of zidovudine. The 2-drug regimen is preferred due to lower toxicity and because nelfinavir powder is no longer available in the United States (see Infant Antiretroviral Prophylaxis and Table 9). • Evaluate need for initiation of maternal therapy postpartum.

Table 6. Clinical Scenario Summary Recommendations for Antiretroviral Drug Use by Pregnant HIV-Infected Women and Prevention of Perinatal Transmission of HIV-1 in the United States (Page 4 of 4)

Clinical Scenario	Recommendations
Infants born to HIV-infected women who have received no ART before or during labor	• Infants born to HIV-infected women who have not received antepartum ARV drugs should receive prophylaxis with a combination ARV drug regimen started as close to the time of birth as possible. Zidovudine[b] given for 6 weeks combined with 3 doses of nevirapine in the first week of life (at birth, 48 hours later, and 96 hours after the second dose) has been shown to be effective in a randomized controlled trial and less toxic than a 3-drug regimen with nelfinavir and laminvudine for 2 weeks and 6 weeks of zidovudine. The 2-drug regimen is preferred due to lower toxicity and because nelfinavir powder is no longer available in the United States (see Infant Antiretroviral Prophylaxis and Table 9). • Evaluate need for initiation of maternal therapy postpartum.

[a] Zidovudine continuous infusion: 2 mg/kg zidovudine intravenously over 1 hour, followed by continuous infusion of 1 mg/kg/hour until delivery.

[b] Zidovudine dosing for infants ≥35 weeks' gestation at birth is 4 mg/kg/dose orally twice daily; for infants <35 weeks of gestation at birth is 1.5 mg/kg/dose intravenously or 2.0 mg/kg/dose orally, every 12 hours, advancing to every 8 hours at 2 weeks of age if ≥30 weeks of gestation at birth or at 4 weeks of age if <30 weeks' gestation at birth.

Table 7. Clinical Scenarios and Recommendations Regarding Mode of Delivery to Reduce Perinatal Transmission of HIV

Clinical Scenario	Recommendations
HIV-infected women presenting in late pregnancy (after about 36 weeks' gestation), known to be HIV infected but not receiving antiretroviral (ARV) medications, and who have HIV RNA level and CD4 cell counts pending but unlikely to be available before delivery.	• Start ARV medications as per Table 6. • Provide counseling on the likelihood that scheduled cesarean delivery will reduce the risk of mother-to-child transmission, if viral suppression cannot be documented prior to 38 weeks. Include information on the increased maternal risks of cesarean delivery, including increased rates of postoperative infection, anesthesia, and other surgical risks. • When the delivery method selected is scheduled cesarean, perform the procedure at 38 weeks' gestation, as determined by last menstrual period and ultrasonography. • Administer continuous intravenous zidovudine beginning 3 hours before scheduled cesarean. • Continue other ARV medications on schedule, as much as possible, before and after surgery. • Use of prophylactic antibiotics at the time of cesarean delivery is recommended.
HIV-infected women who began prenatal care early in the third trimester, are receiving combination ARV drug regimens, and have an initial virologic response but have HIV RNA levels that remain substantially >1,000 copies/mL at 36 weeks' gestation.	• Continue the current combination ARV regimen because the drop in HIV RNA level is appropriate. • Provide counseling on the timing of response to ARV medications and the likelihood that maternal HIV RNA levels may not fall below 1,000 copies/mL before delivery. Consider scheduled cesarean delivery if viral load suppression is not achieved by 38 weeks because of the potential additional benefit in preventing intrapartum transmission of HIV. Inform patients about the increased maternal risks associated with cesarean delivery, including risks related to anesthesia and surgery and increased rates of postoperative infection. • When the delivery method selected is scheduled cesarean, perform the procedure at 38 weeks' gestation, as determined by last menstrual period and ultrasonography. • When the delivery method selected is scheduled cesarean delivery, administer continuous intravenous zidovudine beginning 3 hours before scheduled cesarean. • Continue other ARV medications on schedule, as much as possible, before and after surgery. • Use of prophylactic antibiotics at the time of cesarean delivery is recommended.
HIV-infected women on combination ARV drug regimens with undetectable HIV RNA levels at 36 weeks' gestation.	• Provide counseling on the risk of perinatal transmission of HIV with a persistently undetectable HIV RNA level, which is probably 1% or less, even with vaginal delivery. No evidence currently exists to show that this risk can be lowered further by performing scheduled cesarean delivery. • Risk of complications is increased with cesarean delivery, compared with vaginal delivery, even in the HIV-uninfected population, and the risks must be balanced against the uncertain benefits of cesarean delivery in women with undetectable viral load.
HIV-infected women who have elected scheduled cesarean delivery but present after rupture of membranes at >37 weeks' gestation.	• Start intravenous zidovudine immediately. • Individualize the decision regarding mode of delivery, based on clinical factors such as duration of rupture, anticipated progress of labor, plasma RNA level, and current ARV regimen. • When vaginal delivery is chosen, some clinicians may consider administration of oxytocin, if clinically appropriate, in order to expedite delivery. Scalp electrodes and other invasive monitoring and operative delivery should be avoided, if possible, unless there are clear obstetric indications. • When cesarean delivery is chosen, administration of the loading dose of intravenous zidovudine ideally should be completed prior to the procedure. However, decisions regarding timing of delivery should be individualized.

Table 8. Recommended Intrapartum Maternal and Neonatal Zidovudine Dosing for Prevention of Mother to Child Transmission of HIV

Maternal Intrapartum		
Zidovudine (ZDV)	**Dosing**	**Duration**
ZDV	2 mg per kg body weight intravenously over 1 hour, followed by continuous infusion of 1 mg per kg body weight per hour	Onset of labor until delivery of infant
Neonatal		
Zidovudine (ZDV)	**Dosing**	**Duration**
ZDV	**≥35 weeks gestation:** 4 mg per kg body weight per dose given orally twice daily, started as soon after birth as possible and preferably within 6-12 hours of delivery (or, if unable to tolerate oral agents, 1.5 mg per kg body weight per dose intravenously, beginning within 6–12 hours of delivery, then every 6 hours)	Birth through 6 weeks
ZDV	**<35 to ≥30 weeks gestation:** 2 mg per kg body weight per dose given orally (or 1.5 mg per kg body weight per dose intravenously), started as soon after birth as possible and preferably within 6-12 hours of delivery, then every 12 hours, advanced to every 8 hours at age 2 weeks	Birth through 6 weeks
ZDV	**<30 weeks gestation:** 2 mg per kg body weight per dose given orally (or 1.5 mg/kg/dose intravenously) started as soon after birth as possible and preferably within 6-12 hours of delivery, then every 12 hours, advanced to every 8 hours at 4 weeks of age	Birth through 6 weeks

Table 9. Intrapartum Maternal and Neonatal Dosing for Additional Antiretroviral Drugs in Special Circumstances Based on NICHD-HPTN 040/PACTG 1043 Regimen[1] (Updated September 14, 2011; Erratum issued December 1, 2011) (See Special Considerations Regarding the Use of Antiretroviral Drugs by HIV-Infected Pregnant Women and their Infants for further discussion.)

Maternal Intrapartum/Postpartum		
Antiretroviral (ARV) Drug	**Dosing**	**Duration**
ZDV	2 mg per kg body weight intravenously over 1 hour, followed by continuous infusion of 1 mg per kg body weight per hour	Onset of labor until delivery of infant
Neonatal (initiated as soon after delivery as possible)		
Antiretroviral (ARV) Drug	**Dosing**	**Duration**
2-drug regimen: ZDV + NVP	• ZDV: 4 mg/kg given orally twice daily[1 a, b] • NVP: *Birth weight 1.5–2 kg:* 8 mg per dose given orally *Birth weight >2 kg:* 12 mg per dose given orally	Birth through 6 weeks 3 doses in the first week of life • 1st dose within 48 hrs of birth (birth–48 hrs) • 2nd dose 48 hrs after 1st • 3rd dose 96 hrs after 2nd

Key to Abbreviations: NVP = nevirapine; ZDV = zidovudine

[1] Erratum Issued December 1, 2011; Dosing for the 3-drug regimen is not shown because nelfinavir powder is no longer commercially available in the United States, and the 2-drug regimen is preferred.

[a] NICHD-HPTN 040/PACTG 1043 used ZDV 12 mg given orally twice daily if the birth weight was >2 kg and 8 mg given orally twice daily if the birth weight was 1.5–2.0 kg.

[b] ZDV dosing regimen is for infants ≥35 weeks' gestation. See Table 8 for recommended doses for premature infants.